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Moderators of response to cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care

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Abstract

Background: Stratified medicine aims to improve clinical and cost-effectiveness by identifying moderators of treatment that indicate differential response to treatment. Cognitive Behavioural Therapy (CBT) is often offered as a 'next-step' for patients who have not responded to antidepressants, but no research has examined moderators of response to CBT in this population. We aimed, therefore, to identify moderators of response to CBT in treatment resistant depression.

Methods: We used linear regression to test for interactions between treatment effect and 14 putative moderator variables using data from the CoBalT randomised controlled trial. This trial examined the effectiveness of CBT given in addition to usual care (n = 234) compared with usual care alone (n = 235) for primary care patients with treatment resistant depression.

Results: Age was the only variable with evidence for effect modification (p value for interaction term = 0.012), with older patients benefiting the most from CBT. We found no evidence of effect modification by any other demographic, life, illness, personality trait, or cognitive variable ($p \geq 0.2$).

Conclusions: Given the largely null findings, a stratified approach that might limit offering CBT is premature; CBT should be offered to all individuals where antidepressant medication has failed.

Keywords: Depression, cognitive behavioural therapy, CBT, treatment resistance, moderators, stratified medicine, primary care.

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Introduction

Depression is a major contributor to the global burden of disease and projected to be a leading cause of disability worldwide by 2030 (Mathers and Loncar, 2006). There is good evidence that cognitive behavioural therapy (CBT) is an effective treatment in previously untreated episodes of depression (Butler et al., 2006; Cuijpers et al., 2008). Patients vary considerably in their response to CBT with sizable proportions responding either not at all or only partially. It is therefore clinically useful to identify which patients will respond. Reliable evidence informing this issue remains elusive, however, and clinicians often decide which patients to refer to which treatment based on clinical judgements about patient suitability (Safran, 1990). In line with the current drive towards stratified medicine that aims to target interventions at subgroups of patients who are likely to respond (Hingorani et al., 2013), research is needed to identify reliable moderators or effect modifiers of treatment response. It is important to distinguish between predictors and moderators. Predictors are prognostic factors associated with disease outcomes irrespective of treatment, whereas moderators are associated with differential response to treatments (predictors and moderators are assessed at baseline and are different from mediators that are on the causal pathway (Kraemer et al., 2002)). In other words, a moderator will lead to a smaller or larger difference between active and comparator groups. Understanding of potential moderators is clinically useful, as this would enable clinicians to base treatment choices on the individual's likelihood of benefiting from a given treatment. A variable is established as a moderator by investigating interactions

between that variable and two or more treatment options, ideally within the context of a randomised controlled trial (Brookes et al., 2001). Studies designed specifically to test for interactions are large, expensive, and therefore rare. Using existing data from good quality and well-controlled clinical trials is an efficient and cost-effective alternative, although with the potential for lower statistical power (Button et al., 2012).

Previous studies reporting moderators of response to CBT in controlled trials of adults have used small sample sizes, randomising fewer than 63 patients per CBT arm (Elkin et al., 1995; Farabaugh et al., 2012; Fournier et al., 2009; Leykin et al., 2007; Sotsky et al., 1991), or have compared CBT to antidepressant treatment (Fournier et al., 2009; Leykin et al., 2007). With such small sample sizes these studies were almost certainly underpowered (Brookes et al., 2001), and whilst understanding which of two treatment options is likely to produce the best outcomes is important, in practice, antidepressants and CBT are often prescribed together (Button et al., 2012). There is growing evidence that CBT and antidepressants combined are more effective than either treatment alone (Cuijpers, 2014; Cuijpers et al., 2009b), and that CBT is effective as an adjunct to antidepressants where such medication has failed (Wiles et al., 2013). Moreover, despite guidance in the UK suggesting CBT be offered to all moderately depressed patients, anecdote suggests that in practice CBT is often reserved for those patients who have not responded to antidepressant medication. We have previously examined moderators of response to CBT delivered by a therapist via the internet as an adjunct to usual care that included the option of antidepressants where prescribed (Button et al., 2012). However, no previous research has examined moderators of response to CBT as a 'next-step' treatment for primary care patients who have not responded to antidepressants.

Few previous studies have examined demographic variables as potential moderators of response to CBT in adults using appropriate tests for interaction (Button et al., 2012; Fournier et al., 2009; Sotsky et al., 1991). Fournier and colleagues found that being married, unemployed, and having more antecedent life events were associated with better response to CBT than antidepressants (Fournier et al., 2009). In our previous study, we found that being separated/widowed/divorced and having fewer recent stressful life events were associated with better responses to CBT compared with a waiting list control (Button et al., 2012). Pre-treatment severity of depression is the most reliable moderator of response to CBT in the literature, with the more severely depressed benefiting most. (Button et al., 2012; Driessen et al., 2010; Kiosses et al., 2011; Thompson et al., 2001) There is no previous evidence that history or chronicity of depression are moderators of CBT response (Button et al., 2012; Fournier et al., 2009), and the evidence for co-morbidity as a moderator is mixed (Asarnow et al., 2009; Farabaugh et al., 2012). Assessing individuals' suitability for therapy is an important part of clinical practice, which often focuses on interpersonal skills, personality, and psychological mindedness (Safran, 1990). Personality disorder has been studied in this context, with a meta-analysis of well-designed RCTs finding no evidence of moderation on response to treatments for depression (Kool et al., 2005). There is, however, some evidence that personality traits and dysfunctional attitudes moderate response to CBT relative to pharmacotherapy, with more neurotic individuals and individuals with high dysfunctional attitudes more likely to respond to antidepressants than to CBT (Bagby et al., 2008; Shankman et al., 2013).

Therefore, the aim of the present study was to examine potential moderators of response to CBT given as an adjunct to usual care that included pharmacotherapy as a 'next step'

treatment for patients whose depression had not responded to treatment with antidepressants using data from the CoBalT trial (Wiles et al., 2013). Evidence of moderators in this group will inform decisions concerning which patients unresponsive to medication should be referred for CBT. We therefore examined the modifying effects of demographic, life events, illness, co-morbidity, personality traits and cognitive variables.

Methods

Participants

This study is a secondary analysis of data collected as part of the CoBalT randomised controlled trial examining the effectiveness of cognitive behavioural therapy as an adjunct to usual care (that included pharmacotherapy) for patients with treatment-resistant depression in primary care (Wiles et al., 2013). Definitions of treatment-resistant depression range from non-response to at least 4 weeks treatment with antidepressants (WPA, 1974) to more stringent definitions such as non-response to multiple courses of treatment (Amsterdam and HornigRohan, 1996; Fava, 2003; Fekadu et al., 2009; Thase and Rush, 1997), but there is no universally agreed definition. The CoBalT team therefore chose to operationalise this for the trial in a way that was applicable to UK primary care and reflects the uncertainty about how best to manage depression following non-response to the first line treatment.

Individuals were eligible for the trial if they were aged between 18-75 years, were currently taking antidepressant medication and had been doing so at an adequate dose for at least 6 weeks, scored 14 or more on the Beck Depression Inventory (BDI-II)(Beck et al., 1996) and met the ICD-10 criteria for depression (assessed using the Clinical Interview Schedule –

Revised form, CIS-R (Lewis, 1994; Lewis et al., 1992)). A BDI score of 14 or more indicates a clinical level of depression, with 14-19 considered mild, 20-28 moderate, and ≥29 severe depression. Four hundred and sixty-nine participants were randomised to one of two groups: (1) usual care (n = 235) or (2) CBT in addition to usual care (n = 234), which comprised a maximum of 18 sessions, each lasting 50-60 minutes, with a CBT therapist. Therapists used the CBT for depression treatment manuals (Beck et al., 1979; Beck, 1995; Moore and Garland, 2003). Treatment allocation was stratified by recruitment centre and minimised, with a probability weighting of 0.8 (Brown et al., 2005), according to the following variables: baseline BDI-II score (mild, moderate, severe); whether participant's general practice had a counsellor (yes/no); prior treatment with antidepressants (yes/no) and duration of their current episode of depression (<1 year; 1-2 years; ≥2 years). Minimisation was used in order to achieve balance in these important (design) variables across the treatment arms. Participants were followed up for a year at intervals of three months, with the BDI-II being completed at baseline, six and twelve months. A total of 422 (90%) of participants were followed up at 6 months and 396 (84%) at 12 months.

Outcome

The outcome variable used in the current study was BDI-II score treated as a continuous variable at 6 and 12 months, analysed as a repeated measure to increase power; 427 (91%) of patients provided data for at least one follow up. We treated BDI-II score as a continuous variable in this exploratory study to retain maximum power and ensure comparability of findings with previous studies of effect modification (Button et al., 2012; Fournier et al., 2009). This is in contrast to the main trial paper, where the primary outcome was a binary

variable representing a reduction in BDI-II score of at least 50% compared to baseline (Wiles et al., 2013).

Potential Moderators

We investigated all variables measured prior to randomisation as potential moderators where there was precedent in the literature. The potential moderators were identified from previous research and grouped into three general classes: (1) demographic and life factors; (2) illness characteristics; and (3) personality, cognition and psychological mindedness. We did not investigate patient expectation of outcome or degree of treatment resistance (defined on the basis of duration of present symptoms and past treatment with antidepressant drugs), as these subgroup analyses are reported in the main trial analysis and indicated no evidence that either variable moderated response to CBT (Wiles et al., 2013). All data on potential moderators were collected prior to randomisation.

Demographic and life factors

Age was measured as continuous and categorised into the following groups: (1) <30, (2) 30-39, (3) 40-49 and (4) >49 years for analysis. Level of education was defined as highest educational qualification and categorised as: (1) A level/Higher grade or above, (2) Other qualifications – GCSE or equivalent and (3) No formal qualifications. A-levels are UK national qualifications generally taken at age 18 years, and qualifications at this level are usually required for entry to university or higher education. A-Levels / Higher grade would correspond to 12th Grade in the US Education system. GCSEs are also UK national qualifications generally taken at age 16 years, and mark the end of compulsory education in

the UK. The age at which GSCEs are taken corresponds to 10th Grade in the US system. For marital status the participant selected from the following options: single; separated; divorced; widowed; married/living as married, and for the analysis we categorised marital status as: (1) Single, (2) Married/Living as married and (3) Separated/widowed/divorced. Eight questions selected from the Social and Readjustment Rating Scale (Holmes and Rahe, 1967), dealing with bereavement, separation or divorce, serious illness or injury, victim of crime, problems with the police resulting in a court appearance, debt, disputes with friends/relatives/neighbours and redundancy within the 6 months prior to randomisation were used to measure adverse life events. The number of life events were summed and categorised as: (1) 0 events, (2) 1-2 events and (3) 3 or more events.

Illness characteristics

Two measures of pre-treatment depression severity were used: (i) baseline BDI-II score measured as continuous but dichotomized for analysis, for consistency with previous research (Button et al., 2012), as (1) Severe (BDI-II score > 28) and (2) Less severe (BDI-II score < 29); (ii) baseline CIS-R depression severity as a continuous variable, generated by summing the depression, depressive ideas, fatigue, concentration, and sleep sections of the CIS-R to produce a score ranging from 0 to 21. The BDI-II is not a diagnostic scale, but instead provides a measure of depressive symptom severity. The CIS-R, by contrast, provides diagnoses in line with ICD-10. We include both to provide insight into the robustness of any observed effects. The BDI-II has good psychometric properties (Beck et al., 1988), with an internal consistency 0.9 (Wang and Gorenstein, 2013). History of depression was assessed as part of the CoBalT baseline questionnaire, in terms of self-reported number of previous

episodes of depression and the duration of the current episode. Number of prior episodes of depression was categorised as collected: (1) 0-1 episodes, (2) 2-4 episodes and (3) ≥5 episodes. The duration of the current episode of depression was assessed as a categorical variable as: (1) less than 1 year, (2) 1-2 years and (3) more than 2 years. Anxiety was measured as the score of the CIS-R anxiety section, range 0-4, with higher score indicating more symptoms. Post-traumatic stress disorder was scored as an additive count of symptoms on the Primary Care PTSD Screen (PC-PTSD) with a possible range of 0-4 (Prins et al., 2003) with higher score indicating more symptoms. Longstanding illness was investigated by recording participants' other self-reported illnesses as a categorical variable: (1) No chronic illness, (2) Diabetes, (3) Asthma, (4) Arthritis, (5) Heart disease, (6) High blood pressure, (7) Lung disease, (8) more than one of the above and (9) none of the above but other.

Personality, cognition and psychological mindedness

Dysfunctional attitudes and meta-cognitive awareness were measured as continuous variables by summing participants' responses to the Dysfunctional Attitudes Scale – Short Form, DAS-SF_2 (Beevers et al., 2007) and Meta-cognitive Awareness Questionnaire, MAQ (Teasdale et al., 2001) respectively. Neuroticism was measured using the neuroticism subscale of the "Big Five" Inventory, BFI (John et al., 1991) and examined as a continuous variable as the mean score of the eight test items. Higher score indicates increased neuroticism. The DAS-SF_2, MAQ, and neuroticism subscale all show good internal consistency, at 0.8 (Beevers et al., 2007), 0.7 (Teasdale et al., 2001) and 0.8 (Bech et al., 2012) respectively.

Statistical analysis

Treatment effect is defined as the difference in mean BDI-II outcome scores (as a continuous variable) between the usual care and intervention arms, adjusted for stratification and minimisation (i.e., design) variables. Separate random effects regression models (RRM) were carried out for each potential moderator including an interaction term between the relevant moderator and treatment allocation, adjusting for the stratification and minimisation (design) variables (listed earlier) and time, to test for effect modification on the outcome over 12 months. Further models, containing a three way interaction (moderator by treatment allocation by time) were carried out to investigate whether effect modification varied across time, and all analyses were repeated separately for 6 months and 12 months, but these results are only discussed where they suggest different conclusions from the repeated measures analysis. RMM were also carried out separately for each level of the potential moderators to further illustrate any interaction effects.

We decided to focus on the above approach (i.e., examining each moderator in a separate model) to aid the interpretation of the results. This approach does not account for the potential confounding effects of other effect modifiers, however, which might attenuate, or augment significant relationships (Friedman and Wall, 2005). Therefore, we also ran a single model including all putative moderator variables and their interaction terms.

All RRM analyses used the xtmixed command in Stata version 11. RRM is a variance component model, with observations nested within subjects for the analysis of longitudinal data. Furthermore, RRM is consistent with the analyses conducted in the main trial paper. In order to maximise statistical power, we also examined the results of analyses that treated moderators as continuous variables where data were collected as such - age, baseline severity

(BDI-II), number of previous episodes and life events, whilst recognising that such analyses will be more difficult to interpret.

Results

Baseline characteristics

The randomisation groups were similar in terms of the stratification and minimisation variables (baseline BDI-II score, whether participant's general practice had a counsellor, prior treatment with antidepressants and duration of their current episode of depression (Wiles et al., 2013) and the other potential treatment moderators investigated (Table 1). Regarding the level of treatment-resistance to antidepressants, at randomisation 70% (327) had been prescribed their present antidepressants for more than 12 months, 80% (378) reported their current episode of depression as having lasted more than a year, and 80% (377) had been prescribed antidepressants previously to their current course of medication (Table 1).

It is important to understand if adherence to the intervention, and therefore treatment dose, varied by potential moderators as this could potentially explain any effect modification. The level of adherence to the intervention (defined as the mean number of CBT sessions attended) were generally very similar across the levels of the potential moderators investigated, (Table 1), suggesting that any observed effect modification was not due to differences in treatment adherence. However, there was some variation in education; the more highly educated attended the most sessions (mean 12.5, s.d. 5.9) and those without formal qualifications attended the least (mean 8.6, s.d. 6.5). There was also some variation in adherence by

longstanding physical illness, which is likely due to the low numbers of patients with any given illness.

Main effects of potential moderators on outcome

There was evidence of a main effect of age, regression coefficient = 0.11 (95% CI 0.02, 0.20), p = 0.02, and baseline severity measured on the BDI-II (continuous), regression coefficient = 0.57 (95% CI 0.47, 0.67), p < 0.001, with weaker evidence on the CIS-R β = 0.44 (95% CI -0.00, 0.88), p = 0.05. Older age and higher severity of depression indicated worse general outcome. There was weak evidence for a main effect of longstanding illness (p = 0.08 from the Wald test), and little evidence of main effects of all other potential moderator variables (all p values ≥ 0.14).

Effect modification by potential moderators

The results obtained from the RMM suggested that age and to a lesser extent baseline BDI, were the only variables for which there was any evidence of an interaction between a potential moderator and the intervention. The interaction coefficients became more negative the higher the age category, suggesting that the higher the age category the greater the benefit of treatment (p-value for interaction effect = 0.012; Table 2). This was also consistent with the linear term, treatment × age, with a regression coefficient = -0.24 (95% CI -0.44, -0.04), p = 0.02, implying that age may modify the effectiveness of CBT, with older individuals gaining most treatment-derived benefit. It is worth noting however, that there is no suggestion of any material dis-benefit from CBT at any age.

Regarding baseline severity, there was little evidence of effect modification in the dichotomous (severe/less severe) analysis of BDI-II scores or in the continuous analysis using

the CIS-R score. However, treating baseline BDI-II as a continuous variable we found weak evidence of modification, treatment × BDI interaction regression coefficient = 0.20 (95% CI 0.00, 0.39), p = 0.05, indicating that CBT was less effective as baseline severity increased. However, including the treatment × BDI × time interaction in the RMM weakens the evidence for the severity interaction (p = 0.20), as does separate analysis of outcome at 6 months (p = 0.22) and 12 months (p = 0.10), suggesting that the effect is not robust.

When the RRM analyses were carried out separately at each level of the potential moderator variables the adjusted differences in mean BDI-II scores further demonstrated a lack of effect modification except for age, and baseline severity, as the differences in mean BDI-II scores between the levels of the potential moderators variables were similar, had overlapping confidence intervals and did not show any clear trends (Table 2). For the categorical age variable, however, the confidence intervals were overlapping but the coefficients were consistent with the earlier conclusion regarding this interaction that the older patients benefited most from CBT. Looking at the mean outcome scores (Supplementary Table 1) the younger subgroups of patients had better outcomes irrespective of treatment group, and thus had smaller treatment effects in terms of mean BDI score differences. The three-way treatment × moderator × time interactions suggested that there was little evidence that the relationships between any of the investigated potential moderators and the intervention varied over time (p's $\geq$ 0.07). Analysing life events as continuous found no evidence for moderation (p = 0.58).

The results from the full model combining all putative moderators and their interaction terms were broadly consistent with the results above (i.e., null), except that in the full model there was no evidence for effect modification by age or severity (all p's > 0.12).

Discussion

Summary of main findings

This is the first study to examine moderators of response to CBT as a 'next-step' treatment for primary care patients whose depression had not responded to treatment with antidepressants. The level of non-response to antidepressants was high; the vast majority of our sample (70% -80%) had been prescribed their present antidepressants for more than 12 months, reported their current episode of depression as having lasted more than a year, and had been prescribed antidepressants previously to their current course. Of the fourteen variables assessed, age and to a lesser extent baseline BDI-II score, were the only variables with some statistical evidence for effect modification; older patients benefited the most from CBT, and there was weak evidence that the more severely depressed individuals benefited least. However, our results were not sufficiently precise to conclude either that CBT was, or was not, effective for the younger participants, and the moderation effect for baseline severity was not robust and was in the opposite direction to previous literature (Button et al., 2012). We found no evidence of effect modification by any other demographic variable, life events, longstanding illness/disability, personality trait, cognitive or psychological mindedness variables. We have previously shown that CBT as an adjunct to antidepressants produces better outcomes than antidepressants alone (Wiles et al., 2013). In the absence of strong evidence of moderation of this effect, we should assume that all patients who have not responded to antidepressants will benefit from referral for CBT.

Strengths and Limitations

This is the first study to examine moderators of response to CBT in a difficult-to-treat sample, and the large sample (n = 469), and quality of the CoBalT trial data, is a major strength. However, the limitations associated with post-hoc subgroup analyses should be borne in mind when interpreting our findings (Brookes et al., 2001). Secondary subgroup analyses suffer from low statistical power, but they are also prone to false positive findings due to multiple testing. To retain power in this exploratory analysis we did not control for multiple comparisons. Caution is therefore required when interpreting findings for a single study. Consistent findings across studies are required before we can consider moderators as clinically informative and, ideally, meta-analyses of randomised studies should be conducted using individual patient data to achieve sufficient statistical power. Although our sample size (n =469) is one of the largest clinical trials of CBT to date, it is small for testing interactions, creating uncertainty about the reliability of the estimates. Multiple testing increases the likelihood of chance findings. However, we tested fourteen different variables and only found evidence for one moderator. The variables we report here are the only variables we have examined for moderation.

Number of CBT sessions attended is a relatively crude measure of treatment received, as other factors such as therapist competence, fidelity to the CBT model and use of "active" techniques have been associated with effectiveness in other disorders (Freeman et al., 2013; Norrie et al., 2013). However, our aim is to identify moderators that predict response in a pragmatic sense and we use number of sessions to, albeit crudely, describe adherence by moderator. CBT often focuses on interpersonal factors or relationship issues that might be differentially important for someone who is married, or in a stable relationship, than for

someone who is single. It is unclear how individuals in a stable relationship were captured by marital status in this study as they may have self-identified as "single" or "living as married". Finally, we cannot eliminate the possibility that there are other moderating factors, including those related to previous treatment, which we have not measured or studied in this research.

Comparison of findings with previous literature

We found evidence for effect modification by age, with older patients benefiting the most from CBT. There is no precedent for age as a moderator (Button et al., 2012; Fournier et al., 2009) so we treat our result with caution, as it may be an artefact of multiple testing. In contrast to RCTs of previously untreated episodes of depression, the mean age of patients in CoBalT was higher, with over half the sample being 50 years or older when they entered the study (Wiles et al., 2013). We would not expect this in itself to influence the findings in terms of the pattern of coefficients, especially given the good balance between the trial arms with respect to age. Yet it may have increased our power to detect this particular interaction compared with other studies with a younger age distribution. Alternatively, it may reflect something specific to the treatment resistant population. CBT was most effective for patients over 40 years, and least effective in patients aged 30 to 39 years. All patients improved apart from those in the older subgroups who were in the usual care arm (and therefore did not have the option to receive CBT). This lack of improvement in the usual care arm explains the greater treatment effect observed in the older subgroups, while the younger subgroups had better outcomes irrespective of treatment. It is also worth noting that given the small numbers (n = 61) in the 30 to 39 subgroup, the confidence intervals around the estimate are wide,

providing no evidence for either treatment benefit or harm. Further research is required to assess whether this finding is robust, and explore potential mechanisms.

In contrast with previous research (Button et al., 2012; Fournier et al., 2009; Sotsky et al., 1991), we did not identify marital status or stressful life events as moderators in the present sample. The point estimates for marital status were consistent with single individuals gaining least from CBT, but there was no statistical evidence for effect modification. Number of recent stressful life events has been identified as a potential moderator in two previous studies (Button et al., 2012; Fournier et al., 2009). We previously found individuals with 3 or more recent life events gained the least from CBT compared to waiting list control, where around half of individuals in both arms were prescribed antidepressants. In contrast, Fournier and colleagues found individuals with more stressful life events gained most benefit from CBT but this was in direct comparison with antidepressant medication The estimates for life events in this study offers little support to either of the previous findings (Button et al., 2012; Fournier et al., 2009), which taken together suggest that number of recent life events is not a reliable moderator of response to CBT, at least in this population that is concurrently taking antidepressant medication. However, research suggests that life events become less important in the aetiology of depression with increased recurrence (Lewinsohn et al., 1999), so it may be inappropriate to generalise the findings from the chronic population in CoBaLT to other trials of CBT for depression.

Previous studies suggest pre-treatment severity of depression is the most reliable moderator of response to CBT, with the more severely depressed benefiting most (Button et al., 2012; Driessen et al., 2010). However, meta-analytic findings that rely on aggregate data (Cuijpers et al., 2008) and issues of scaling confuse these severity findings, which may be an artefact of

assessing outcomes using continuous measures. For example, a 5-point reduction in scores for someone whose baseline was 50 is a proportionally smaller improvement than is a 5-point change from a baseline of 15. We found weak evidence of an interaction with baseline severity as measured on continuous BDI-II, but not in the categorical or CIS-R analyses, which suggests that the interaction is not robust. Moreover, this effect was in the opposite direction to that predicted by the previous literature so we also treat this result with caution. This may reflect the nature of our treatment resistant sample; in CoBalT, patients were selected for their non-response to antidepressants. In our previous study (Button et al., 2012), less severe depressions, as assessed by symptoms, improved equally well irrespective of receiving CBT or waiting list control; in contrast, CBT was particularly effective for severe depression, which did not improve in the waiting list arm. The participants in CoBalT had a poorer outcome than in our previous study as we selected patients through the resistance of their symptoms to pharmacotherapy. This may explain the different pattern of effect modification by severity of symptoms in this group. It is of note, however, that baseline symptom severity in CoBalT was similar to other RCTs of depression in the UK (Chalder et al., 2012; Kessler et al., 2009; Lewis et al., 2011; Wiles et al., 2012). The CoBalT sample was nevertheless more "severe" in terms of chronicity, number of previous episodes, comorbidities and non-response to medication (Wiles et al., 2013). This suggests that to capture the extent of illness that we see clinically, we need to account for both severity and chronicity, especially in those whose symptoms are resistant to antidepressants.

Assessing individuals' suitability for therapy is an important part of clinical practice, which often focuses on interpersonal factors, personality, and psychological mindedness (Safran, 1990). However, the literature on this area is based more on clinical opinion (Safran, 1990)

than empirical evidence. Consistent with previous research assessing personality traits in untreated episodes of depression (Fournier et al., 2009; Spek et al., 2008), we found no evidence that neuroticism was a moderator of response to CBT in treatment resistant individuals. Patients with lower dysfunctional attitudes have been found to do better in treatment arms (CBT and antidepressants) relative to a placebo tablet (Sotsky et al., 1991), whereas individuals with high dysfunctional attitudes have been found to do better on medication that psychotherapy (Shankman et al., 2013). However, other studies found no evidence for effect modification by dysfunctional attitudes (Fournier et al., 2009; Jacobs et al., 2009). In our sample, neither dysfunctional attitudes nor meta-cognitive awareness were associated with differential response. Therefore, the practice of selecting patients for CBT based on assessments of personality and psychological mindedness remains empirically unsupported. Indeed, such practice may put in place unprecedented barriers to individuals receiving CBT and may contribute to the perceived inequalities in psychotherapy provision (Jokela et al., 2013).

Clinical implications

Combined CBT and pharmacotherapy are more effective than either treatment alone (Cuijpers, 2014; Cuijpers et al., 2009a). However, antidepressants are often prescribed as the first-line treatment for adults with moderate to severe depression, with anecdotal evidence suggesting that, in practice, CBT is often reserved for those patients where medication has failed. CBT as an adjunct to pharmacotherapy is an effective 'next step' treatment for patients whose depression has not responded to treatment with antidepressants (Wiles et al., 2013). However, to further improve patients outcomes by tailoring treatment in line with stratified

medicine (Hingorani et al., 2013), it is helpful understand if there are any factors associated with differential treatment response in this difficult to treat group. We found that response to CBT differed with age, with little evidence that patients under 39 years of age were benefitting from treatment. However, these younger patients had a better outcome and lower depression scores at the end of the trial than the older participants. Given the small numbers of patients and wide confidence intervals in this subgroup, we caution against using age to inform treatment decisions until further research replicates this effect. We have found no evidence to suggest that non-response varied systematically with other patient characteristics. Therefore, we suggest that CBT be offered to all individuals whose depression has not responded to treatment with antidepressant medication.

Research implications

The aims of stratified medicine are laudable and identifying moderators is useful if pursuing stratified models of care. However, as our findings indicate, there is little reliable evidence of differential response from the relatively comprehensive set of moderators that has been examined in the literature to date. One reason for this might be the lack of understanding of the mechanisms of action by which various treatments work. Studies that examine mediators of treatment response may be useful in this regard and may provide a more detailed understanding of why a treatments works. This in turn may inform modifications to interventions in order to improve effectiveness for a broad range of patients.

Conclusions

The evidence to date does not support a stratified approach to prescribing CBT in depressed patients who have not responded to antidepressants, and we suggest therefore that CBT is offered to all patients in this group. There are potential benefits of stratified medicine for patients, and further research into moderators of response to CBT is required. Convincing evidence of moderators of response to CBT may require much larger studies with confirmatory findings and this may need individual patient data meta-analyses. However, it is worth questioning the clinical utility of identifying effect modifiers if the size of treatment effect modification is so small that obtaining reliable evidence requires huge studies. In the light of this, our results suggest that CBT should be offered to all those who have not responded to antidepressant medication.

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Table 1. Comparison of baseline characteristics between randomisation groups, and adherence to CBT intervention by putative moderator variables

Characteristic	Usual care *(n=235)*	Intervention *(n=234)*	Number of CBT sessions attended mean (SD)
Demographic and life factors:			
Centre: *n (%)*			
Bristol	95 (40.4%)	95 (40.6%)	
Exeter	82 (34.9%)	79 (33.8%)	
Glasgow	58 (24.7%)	60 (25.6%)	
GP practice has a counsellor: *n (%)*	116 (49.4%)	112 (47.9%)	
Female: *n (%)*	178 (75.7%)	161 (68.8%)	
Age (continuous): *mean (SD)*	50 yrs (11.5)	49.2 yrs (11.9)	
Age (categories): *n (%)*			
<30	11 (4.7%)	20 (8.6%)	11.0 (6.4)
30-39	32 (13.6%)	29 (12.4%)	10.7 (6.6)
40-49	69 (29.4%)	64 (27.4%)	11.0 (6.3)
>49	123 (52.3%)	121 (51.7%)	11.6 (6.2)
Highest level of education: *n %*			
A Level/Higher Grade or above[a]	105 (45.5%)	112 (48.3%)	12.5 (5.9)
Other Qualifications - GCSE or equivalent	67 (29.0%)	63 (27.2%)	11.5 (5.9)
No formal qualifications	59 (25.5%)	57 (24.6%)	8.6 (6.5)
Marital status: *n (%)*			
Single	45 (19.2%)	44 (18.8%)	9.9 (6.6)
Married/living as married	128 (54.5%)	120 (51.3%)	11.6 (6.4)
Separated/divorced/widowed	62 (26.4%)	70 (29.9%)	11.5 (5.8)
Life events in the past 6 months: *n (%)*			
0 events	71 (30.2%)	62 (26.5%)	11.0 (6.2)
1-2 events	135 (57.5%)	138 (59.0%)	11.5 (6.2)
≥3 events	29 (12.3%)	34 (14.5%)	10.7 (6.8)
Illness characteristics:			
BDI-II score: *mean (SD)*	31.8 (10.5)	31.8 (10.9)	

BDI-II severity group: *n (%)*			
Less severe	103 (43.8%)	102 (43.6%)	10.8 (6.0)
Severe	132 (56.2%)	132 (56.4%)	11.6 (6.4)
CIS-R depression severity score: *mean (SD)*#*	14.9 (2.9)	14.8 (3.1)	Low 11.1 (6.0) High 11.3 (6.5)
Number of prior episodes of depression: *n %*			
0-1 episodes	45 (19.2%)	46 (19.7%)	10.5 (6.4)
2-4 episodes	61 (26.0%)	72 (30.8%)	10.7 (6.4)
≥5 episodes	129 (54.9%	116 (49.6%)	11.9 (6.1)
Duration of current episode of depression: *n (%)*			
<1year	52 (22.1%)	58 (24.8%)	10.2 (6.6)
1-2 years	43 (18.3%)	40 (17.1%)	12.0 (6.1)
>2 years	140 (59.6%)	136 (58.1%)	11.5 (6.1)
Previously prescribed antidepressants: *n (%)*	190 (80.9%)	187 (79.9%)	
Anxiety score: *mean (SD)*	2.4 (1.5)	2.5 (1.5)	
Post Traumatic Stress Disorder score: *mean (SD)**	2.1 (1.5)	2.0 (1.5)	Low 10.7 (6.5) High 11.6 (6.0)
Long-standing illnesses: *n (%)*			
No chronic illness	54 (23.0%)	64 (27.4%)	10.8 (6.3)
Diabetes	6 (2.6%)	10 (4.3%)	7.8 (7.2)
Asthma	17 (7.2%)	11 (4.7%)	11.5 (5.6)
Arthritis	19 (8.1)%	19 (8.1%)	10.7 (7.6)
Heart disease	4 (1.7%)	5 (2.1%)	16.0 (2.9)
High blood pressure	16 (6.8%)	11 (4.7%)	12.4 (4.1)
Lung disease	4 (1.7%)	1 (0.4%)	4.0 (NA)
More than one of the above	44 (18.7%)	35 (15%)	10.7 (6.4)
None of the above but other	71 (30.2%)	78 (33.3)	12.0 (6.0)
<u>Personality, cognition and psychological mindedness:</u>			
Dysfunctional attitudes score: *mean (SD)**	36.9 (10.6)	35.8 (11.0)	Low 10.4 (6.5) High 12.1 (5.9)
Meta-cognitive awareness score: *mean (SD)**	37.4 (7.6)	37.5 (7.7)	Low 11.7 (6.2) High 10.8 (6.3)

Neuroticsm score: *mean (SD)**	4.1 (0.6)	4.0 (0.7)	Low 10.4 (6.5) High 12.0 (5.9)

[a]A-levels are UK national qualifications generally taken at age 18 years, and qualifications at this level or equivalent are usually required for entry to university/higher education

* Continuous variables were median split to produce Low and High categories

[#] Low and High categories defined as a score of less than 2 and 2 or more respectively

Table 2. Treatment effect (*b)* averaged over both follow-up times for each level of potential moderator from random effect regression models (RRM) after adjustment for design variables.

Moderator	*n*	*b*[a]	95% CI	*p*[b]
Demographic and life factors:				
Age				0.012
<30	32	-2.4	(-8.1, 3.3)	
30-39	50	-0.5	(-7.0, 6.0)	
40-49	112	-5.0	(-8.9, -1.1)	
>49	209	-6.6	(-9.4, -3.9)	
Highest level of education				0.43
A Level/Higher Grade or above	198	-4.6	(-7.5, -1.7)	
Other Qualifications - GCSE or equivalent	118	-3.3	(-7.7, 1.1)	
No formal qualifications	85	-7.5	(-12.0, -3.0)	
Marital status				0.39
Single	67	-2.5	(-7.3, 2.4)	
Married/living as married	213	-6.1	(-8.8, -3.3)	
Separated/divorced/widowed	123	-5.0	(-9.2, -0.7)	
Life events in the past 6 months				0.93
0 events	108	-5.0	(-9.0, -1.0)	
1-2 events	236	-5.7	(-8.4, -3.1)	
≥3 events	59	-6.9	(-12.2, -1.5)	
Illness characteristics:				
Baseline BDI-II severity				0.56
Less severe	174	-5.8	(-8.1, -3.5)	
Severe	229	-4.6	(-7.8, -1.3)	
Baseline CIS-R depression severity*				0.91
Low	177	-5.4	(-8.0, -2.8)	
High	226	-5.1	(-8.2, -2.0)	
Number of prior episodes of depression				0.93
0-1 episodes	73	-5.2	(-10.2, -0.2)	
2-4 episodes	126	-5.5	(-9.1, -1.9)	
≥5 episodes	204	-4.7	(-7.7, -1.7)	
Duration of current episode of depression				0.72

<1year	101	-6.1	(-10.2, -2.0)	
1-2 years	68	-3.5	(-8.4, 1.4)	
>2 years	234	-5.2	(-7.9, -2.5)	
Anxiety score[#]				0.82
Low	121	-4.6	(-7.9, -1.3)	
High	282	-5.3	(-7.9, -2.8)	
Post Traumatic Stress Disorder score*				0.36
Low	161	-3.5	(-6.6, -0.5)	
High	242	-5.9	(-8.7, -3.2)	
Illnesses				0.20
No chronic illness	168	-2.4	(-6.8, 2.0)	
Diabetes	17	1.5	(-8.9, 11.9)	
Asthma	19	-8.4	(-18.5, 1.7)	
Arthritis	29	-1.3	(-8.7, 6.1)	
Heart disease	10	-15.4	(-34.5, 3.7)	
High blood pressure	19	-10.1	(-22.8, 2.5)	
Lung disease	2	0	omitted	
More than one of the above	61	-9.6	(-15.0, -4.2)	
None of the above but other	139	-4.9	(-8.2, -1.6)	
Personality, cognition and psychological mindedness:				
Dysfunctional attitudes score*				0.46
Low	189	-5.6	(-8.4, -2.8)	
High	214	-4.7	(-7.7, -1.7)	
Meta-cognitive awareness score*				0.23
Low	183	-8.2	(-11.5, -4.8)	
High	220	-3.0	(-5.7, -0.3)	
Neuroticism score*				0.39
Low	194	-3.3	(-6.2, -0.4)	
High	209	-6.4	(-9.4, -3.3)	

[a] Values represent treatment effects, that is differences in mean BDI-II scores between randomisation groups, as estimated from random effect regression models carried out at each level of moderator with the repeated measure of follow-up time and adjustment for design

variables. Negative values represent more desirable outcomes (i.e. Greater treatment-derived benefit). Continuous variables were median split to produce Low and High levels.

[b] *P* values for formal test of treatment effect modification for each moderator from random effect regression model testing moderator x treatment interaction with the repeated measure of follow-up time and adjustment for design variables and the moderator x treatment x time interaction. Treatment effects varied little over time (P's > 0.07). Where there are three or more subgroups, *p* values are based on Wald tests. Continuous variables were treated as continuous.

Low and High categories defined as a score of less than 2 and 2 or more respectively.

Supplementary Table 1. Adjusted differences in mean BDI-II score between randomisation groups to illustrate further any interaction effects

Moderator	Baseline				6 months				12 months			
	Intervention		Usual care		Intervention		Usual care		Intervention		Usual care	
	n	*Mean*	*n*	*Mean*	*n*	*Mean*	*n*	*Mean*	*n*	*Mean*	*n*	*Mean*
Demographic and life factors:												
Age												
<30	20	31.7	11	35.4	17	19.2	11	20.2	15	15.4	10	15.3
30-39	29	33.7	32	32.6	26	20.8	28	22.2	24	17.8	24	16.0
40-49	64	33.1	69	33.5	57	20.7	61	27.1	55	18.1	56	22.5
>49	121	30.6	123	30.4	106	17.5	113	24.1	103	16.5	108	23.1
Highest level of education												
A Level/Higher Grade or above	112	31.0	105	31.0	101	18.8	93	23.0	97	15.8	93	20.7
Other Qualifications - GCSE or equivalent	63	32.2	67	31.2	60	19.7	63	23.6	58	17.5	56	19.8
No formal qualifications	57	33.1	59	34.5	44	18.6	53	28.7	41	19.6	45	25.3
Marital status												
Single	44	33.5	45	31.6	35	22.9	40	24.5	32	19.5	39	19.4
Married/living as married	120	32.4	128	31.3	109	18.7	114	23.5	104	16.2	109	22.4
Separated/divorced/widowed	70	29.5	62	33.2	62	17.1	59	26.5	61	17.2	50	21.8
Life events in the past 6 months												
0 events	62	29.4	71	31.4	55	16.3	64	21.7	53	15.8	61	20.7
1-2 events	138	32.4	135	31.4	120	19.7	121	24.9	116	17.6	113	22.1

≥3 events	34	33.6	29	35.0	31	20.7	28	29.1	28	17.1	24	22.3
Illness characteristics:												
Baseline BDI-II severity												
Less severe	102	22.5	103	22.1	88	12.4	97	18.8	86	11.9	93	16.5
Severe	132	38.9	132	39.4	118	23.8	116	29.3	111	21.0	105	26.2
Baseline CIS-R depression severity*												
Low	102	25.3	101	25.3	90	14.6	96	19.4	87	12.3	89	17.6
High	132	36.8	134	36.7	116	22.3	117	28.7	110	20.8	109	25.0
Number of prior episodes of depression												
0-1 episodes	46	32.5	45	30.0	38	20.2	40	24.5	35	17.1	39	22.6
2-4 episodes	72	29.7	61	27.8	64	18.8	59	22.4	62	14.8	53	19.9
≥5 episodes	116	32.7	129	34.4	104	18.5	114	25.6	100	18.4	106	22.2
Duration of current episode of depression												
<1year	58	29.2	51	28.4	51	16.8	48	21.9	50	12.8	45	18.7
1-2 years	40	30.5	43	31.1	35	20.5	39	23.5	33	16.4	38	21.6
>2 years	136	33.2	140	33.3	120	19.4	126	25.8	114	19.1	115	22.8
Anxiety score#												
Low	67	26.1	65	26.8	60	16.0	60	20.8	61	15.2	57	20.2
High	167	34.0	170	33.8	146	20.1	153	26.0	136	17.9	141	22.3

Post Traumatic Stress Disorder score*												
Low	93	28.4	87	28.2	81	16	81	21.2	80	16.5	77	17.9
High	141	34.0	148	34.0	125	20.8	132	26.5	117	17.4	121	24.0
Longstanding illnesses												
No chronic illness	64	28.5	54	31.8	55	18.2	48	20.9	52	14.8	45	18.9
Diabetes	10	30.9	6	35.8	10	27.7	6	29.8	7	20.4	6	28.3
Asthma	11	35.3	17	32.6	9	13.2	13	21.0	10	17.3	13	22.3
Arthritis	19	27.1	19	28.9	15	20.2	17	22.2	14	18.7	16	23.5
Heart disease	5	40.8	4	40.5	5	29.4	4	35.5	5	25.6	3	25.7
High blood pressure	11	36.2	16	29.7	9	11.8	15	25.7	10	14.0	13	27.3
Lung disease	1	16.0	4	30.8	1	6.0	4	21.3	1	9.0	4	21.8
More than one of the above	35	36.7	44	32.8	31	20.9	41	28.8	30	20.2	38	25.8
None of the above but other	78	32.0	71	31.5	71	18.3	65	24.5	68	16.5	60	18.4
Personality, cognition and psychological mindedness:												
Dysfunctional attitudes score*												
Low	115	29.2	111	28.4	97	18.0	99	22.7	92	15.9	94	21.4
High	119	34.2	124	34.9	109	19.8	114	26.1	105	18.0	104	21.9
Meta-cognitive awareness score*												
Low	104	33.0	105	34.2	96	18.2	92	26.2	87	15.7	84	24.0
High	130	30.7	130	29.9	110	19.6	121	23.2	110	18.0	114	19.9

Neuroticism score*												
Low	115	28.6	102	27.8	99	17.8	93	21.0	95	15.7	89	19.9
High	119	34.8	133	34.9	107	20.0	120	27.6	102	18.3	109	23.1

* Continuous variables were median split to produce Low and High categories.

Low and High categories defined as a score of less than 2 and 2 or more respectively.